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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

NOTIFICATION DATE	DELIVERY MODE
07/30/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/564,012	EGOROVA-ZACHERNYUK, TATIANA A.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2009 and 26 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-15 and 17-40* is/are pending in the application.

4a) Of the above claim(s) *17-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-15 and 31-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/23/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 13-15 and 17-40 as recited in the 12/23/09 listing remain pending in the current application, of which claims 13-15 and 31-40 are being considered on their merits. Claims 17-30 remain withdrawn from consideration at this time. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Election/Restrictions

Applicant's election of the species "*Hansenula*", "*Galderia*", "*Cyanidium*", and "one or more of glucose, fructose, and sucrose" in the reply filed on 6/17/10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim 13 is directed in part to an invention that is independent or distinct from the invention originally claimed for the following reasons: It includes an embodiment in which the biomolecule is "a molecule that is naturally synthesized by the mammalian or insect cells." Had the original claims included such a limitation, the examiner would have imposed a species election, because all biomolecules are not functional equivalents for each other. For example, glucose is a biomolecule, but it has a completely different structure and function than a protein. See PCT Rule 13.2 and PCT Administrative Instructions, Annex B, Part 1(f)(I)(B)(2). Since applicant has received an

action on the merits for the originally presented invention, *i.e.*, a method in which the biomolecule is a protein, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 13 will be examined to the extent that it reads on an embodiment in which the biomolecule is a protein. See 37 CFR 1.142(b) and MPEP § 821.03. Claim 31 will be examined to the extent it reads on the yeast *Hansenula*. Claim 37 will be examined to the extent it reads on the red alga *Cyanidium*.

Claim Objections

Claim 37 is objected to because of the following informalities: it omits the word "claim" at line 1, i.e. "A method according to claim 33.". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13 and 31-40 are/remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making proteins from recombinant DNA constructs that are uniformly isotopically labeled on C, H, and O atoms, does not reasonably provide enablement for making isotopically labeled biomolecules of any sort other than proteins or for making non-recombinant isotopically labeled proteins. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims are broadly drawn to making a biomolecule in which about 95% or more of the atoms are isotopically labeled (see page 7, lines 8-12, of as-filed specification) by culturing mammalian or insect cells. The term “biomolecule” must be reasonably interpreted as including any and all molecules that have any effect on any biological system, i.e. any molecule. See M.P.E.P. § 2111.01. Furthermore, applicant has amended claim 13 to encompass virtually any biomolecule, e.g. proteins, nucleic acids, and natural products.

Even if the scope of the biomolecule is limited to proteins, the specification cannot fully enable the claims. The specification is limited to methods of producing recombinant proteins from genetically modified insect and mammalian cells; the skilled artisan would have required undue experimentation at the time of the invention to identify conditions conducive to the production of bacterial proteins in mammalian or

plant cells, for example. Similarly, applicant does not indicate that the medium of Example 6 affects the expression pattern of any proteins naturally produced by mammalian and/or insect cells.

Applicants present a working embodiment (pages 55-57) in which ^{13}C- and ^{15}N-labeled aquaporin and histamine 1 receptor are produced in Sf9 insect cells by culturing them in a particular medium (described in section 6.1.2 at page 49) and another in which ^{13}C- and ^{15}N-labeled histamine 1 receptor is produced in CHO cells by culturing them in another medium (described in section 6.2.3 at page 54). While a narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

Applicants allege that growing mammalian proteins in cells is well known. See 12/23/09 reply, page 10. Applicant alleges that producing recombinant proteins and endogenous proteins "should" face identical challenges. See reply, page 10. These arguments have been fully considered, but they are not persuasive of error.

Applicant has provided no evidence for the statement that "it is generally known in the art that mammalian and insect cells are very capable of producing mammalian proteins." There is also no evidence for applicants' arguments that "there should be no difference between the enablement of recombinant proteins and endogenous proteins" and that "there is no reason to assume that the cells would not express their normal

repertoire of endogenous proteins." These arguments are merely the argument of counsel and are unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-438 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 is drawn to the method of claim 13, "further comprising" additional steps. It is not clear how these steps relate to the steps within step (a) of claim 13. The steps in claim 33 appear to replicate the steps of claim 13. Clarification is required.

Furthermore, step (iv) in claim 33 refers to "a mineral medium which supports growth of the organism," but it is not sure whether this organism is the one in step (iv), step (i) in claim 13, or both. It is not clear whether the organism of step (v) is the same as that of step (iv) and step (i).

Because claims 34-38 depend from indefinite claim 33 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13, 31, 32, and 40 are/remain rejected under 35 U.S.C. 102(b) as being anticipated by Hansen et al. (1992, *Biochemistry* 31: 12713-12718).

Hansen teaches culturing Sp2/0 mammalian hybridoma cells transfected with a urokinase-expressing construct (page 12713, column 2) in a media containing acid-hydrolyzed bacterial and algal extracts that have been labeled with ^{13}C and ^{15}N, then recovering the labeled urokinase (page 12714, column 1). The urokinase produced using Hansen's method allows for study with NMR techniques (page 12715, column 1, and page 12717). Hansen teaches that isotopically labeled protein must be >95% enriched with radioisotopes to be suitable for NMR study (page 12713, column 1).

Claim 13 requires growing cells in a nutrient medium that is described wholly using product-by-process limitations. M.P.E.P. § 2113 reads, "Product-by-process

claims are not limited to the manipulations of the recited steps, only the structure implied by the steps."

The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)

The use of 35 U.S.C. §§ 102 and 103 rejections for product-by-process claims has been approved by the courts. "[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Once a product appearing to be substantially identical is found and an art rejection made, the burden shifts to the applicant to show an unobvious difference. In

this case, the media of Hansen is made by growing bacteria and algae in a labeled medium and promotes production of an isotopically labeled mammalian protein, urokinase, from mammalian cells. The product-by-process limitations in claim 13 (steps (i)-(iii)) only clearly require that the nutrient medium comprise autolyzed, 95% labeled biomass. This rejection might be overcome by a substantive evidentiary showing that the selection of the source of biomass is critical or by an amendment to the claims clearly distinguishing the structure of the required nutrient medium from that of Hansen.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (1992, *Biochemistry* 31: 12713-12718) taken in view of Agre et al. (1998, U.S. Patent 5,741,671; reference A).

Hansen teaches culturing Sp2/0 mammalian hybridoma cells transfected with a urokinase-expressing construct (page 12713, column 2) in a media containing acid-hydrolyzed bacterial and algal extracts that have been labeled with ^{13}C and ^{15}N, then recovering the labeled urokinase (page 12714, column 1). The urokinase produced using Hansen's method allows for study with NMR techniques (page 12715, column 1, and page 12717). Hansen teaches that isotopically labeled protein must be >95% enriched with radioisotopes to be suitable for NMR study (page 12713, column 1).

Hansen does not teach expressing a membrane protein.

Agre teaches expressing the membrane receptor aquaporin-5 using recombinant DNA constructs *in vitro* and *in vivo*. See Examples 10 and 11 at columns 33-34. Agre teaches isolating aquaporin-5 protein from cells. See Example 1 at columns 19-20. Agre teaches that aquaporin-5 may be produced in any of numerous expression hosts, including mammalian cells. See column 11, lines 35-46.

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting Agre's aquaporin-5 for Hansen's urokinase because Agre teaches methods for expressing aquaporin-5 from recombinant DNA and for recovering aquaporin-5 protein from mammalian cells. The skilled artisan would have been motivated to make the substitution in order to produce purified aquaporin-5 for use in *in vitro* studies of aquaporin permeability, which Agre teaches is useful for discovering compounds that aid in treating dry eye. See column 12.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute Agre's aquaporin-5 for Hansen's urokinase because Agre teaches methods for producing recombinant aquaporin-5 and for isolating aquaporin-5 protein from cells, and because Agre teaches that aquaporin-5 may be produced in mammalian cells. Hansen's SP2/0 cells are a mammalian cell expression system.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claims 33-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (1992, *Biochemistry* 31: 12713-12718) taken in view of Heifetz et al. (1990, U.S. Patent 4,929,706; reference B) and Reckel et al. (1986, U.S. Patent 4,595,654; reference C).

The teachings of Hansen are relied upon as above.

Hansen does not specifically teach a culture medium comprising lipids or any one of glucose, fructose, and sucrose. Hansen does not teach a culture medium having components isolated from the sources recited in the claims or using the steps recited in the claims.

Heifetz teaches that at the time of the invention, it was well known to include lipids in culture media for hybridoma cells to promote the cells' growth. See column 2, lines 48-62. Heifetz teaches growing hybridoma cells in a mixture of DME and F-12 media. See column 28, lines 31-34.

Reckel teaches that the DME of Heifetz inherently contains glucose. See column 12, lines 22-27.

Claim 13 requires growing cells in a nutrient medium that is described wholly using product-by-process limitations. M.P.E.P. § 2113 reads, "Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps." Once a product appearing to be substantially identical is found and an art rejection made, the burden shifts to the applicant to show an unobvious difference. In this case, the media of Hansen is made by growing bacteria and algae in a labeled medium and promotes production of an isotopically labeled mammalian

protein, urokinase, from mammalian cells. The product-by-process limitations in claim 13 (steps (i)-(iii)) only clearly require that the nutrient medium comprise autolyzed, 95% labeled biomass. Claim 33 requires that the medium comprise lipids and hydrolyzed amino acids. This rejection might be overcome by a substantive evidentiary showing that the selection of the sources of biomass and/or lipids are critical or by an amendment to the claims clearly distinguishing the structure of the required nutrient medium from that of Hansen.

A person of ordinary skill in the art would have had a reasonable expectation of success in adding the lipids of Heifetz to the culture medium of Hansen because Heifetz teaches including lipids in hybridoma culture medium. The skilled artisan would have been motivated to include lipids because Heifetz teaches that lipids promote hybridoma cell growth.

The skilled artisan would have had a further reasonable expectation of success in including glucose in the media of Hansen because Heifetz teaches culturing hybridoma cells in serum-free, glucose-containing DME media. The skilled artisan would have been motivated to include glucose because Heifetz teaches that glucose-containing DME media permits hybridoma growth for months of serial culture.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to include lipids and glucose in the media of Hansen because Heifetz teaches that these components promote and permit hybridoma growth.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Response to Arguments

Applicant's comments regarding the art rejections of record have been considered to the extent they pertain to the new art rejections. Applicant alleges that Hansen's media differs structurally from the media used in the instant method. Specifically, applicant alleges that Hansen's media is made by excluding components above a certain size and that this difference distinguishes the media of the claims, since Hansen teaches away from including large components. See reply, pages 12-13. These arguments have been fully considered, but they are not persuasive of error.

Hansen's method does not, as applicant alleges, require filtering the amino acids to remove components over 500kDa. Hansen teaches trying "numerous procedures" for yielding the culture media and indicates that removing components above 500kDa "improved cell growth the most" compared to other methods. See page 12715, column 2. Figure 1 demonstrates that unfiltered amino acids promote growth of hybridoma cells, as required by claim 13, step (a).

A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Nonpreferred embodiments constitute prior art. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same

use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). See M.P.E.P. §2123. The fact that filtering the amino acids improves the amino acids' ability to promote growth does not constitute a teaching away, as set forth above.

No claims are allowed. No claims are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is (571)272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651